Remarks

No claims have been amended in this response.

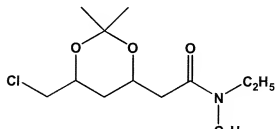
1. Rejection under 35 U.S.C. § 103(a)

The Examiner has maintained his rejection of claims 1-11 under 35 U.S.C. § 103(a) as allegedly unpatentable over WO 02/06266 A1 to Kooistra *et al.* ("Kooistra"). In responding to Applicants' submissions supporting patentability of the pending claims as detailed in the response filed on October 29, 2007, the Examiner points to selected sections of Kooistra in an attempt to demonstrate that regardless how an individual base is utilized in the described processes, "there is a motivation for choosing an alternative selection of the base, which is within the purview of the skilled artisan..." (page 4 of the Office Action). In responding to Applicants' submission that there are significant advantages to using N-methylmorpholine (NMM) as compared to triethylamine when carrying out the acid chloride to ester reaction, the Examiner indicated that any unexpected results should be introduced in the form of a declaration.

As submitted in the earlier filed response, Applicants submit that page 5, line 24 to page 6, line 2 of Kooistra teaches that triethylamine and dimethylaminopyridine (DMAP) are exemplary bases to be used for generating an acid chloride. The only reference to the use of N-methylmorpholine (NMM), which is a feature of the claims of the subject application, is in relation to a different type of process, which is believed to proceed by way of the pivaloyl ester intermediate. Applicants' independent claim 1 recites contacting the generated acid chloride with an alcohol of formula R^2OH in the presence of N-methylmorpholine. Kooistra does not teach or suggest the use of N-methylmorpholine as an aid in forming an ester from an acid chloride. Rather, Kooistra only teaches the use of N-methylmorpholine as an aid in a pivaloyl chloride / t-butanol reaction. As evidence that the pivoloyl chloride / t-butanol / N-methylmorpholine does not proceed through an acid chloride intermediate, Applicants previously submitted for the Examiner's consideration a copy of the Bull. Chem. Soc. Japan article that was cited by Kooistra in referencing this reaction. The article supported Applicants' position that a mixed anhydride, rather than an acid chloride, is generated as an intermediate in the esterification

process. Applicants submitted that in light of this Bull. Chem. Soc. Japan article, it was clear that the section of the Kooistra specification cited by the Examiner for its alleged teaching of the formation of an acid chloride, actually does not proceed through an acid chloride and that a person of ordinary skill in the art would therefore not be motivated to use a base that is taught for a process that is significantly different from the one of interest, especially when the same reference describes a base that is used in a similar process. Stated differently, there would be no motivation for a person of ordinary skill in the art to use NMM for converting an acid chloride into an ester, when Kooistra teaches triethylamine or DMAP as the base of choice for such a conversion, while NMM is described only in a significantly different type of transformation.

Unexpectedly, Applicants have found that there are significant advantages to using NMM when carrying out the acid chloride reaction on a large scale. Applicants submit herewith for the Examiner's consideration a declaration by Dominique Monique Charles Callant under 37 C.F.R. 1.132 that details this unexpected result. Experiments carried out using triethylamine (a base recommended by Kooistra in relation to this particular transformation), gave yields in the range of 40 to 90% (see the table depicted in the declaration), along with the undesired by-product (2) shown below, where a portion of the triethylamine molecule has become incorporated into the dioxane substrate:



(2)

In contrast, when using NMM is used as the base, yields have been observed to be consistently above 85% (*e.g.*, 88% in Example 2 of the subject application), with minimal formation of undesired by-products. The reproducibility of such an excellent and clean yield for this transformation makes NMM particularly suitable for use on large scale. This advantage of

NMM could not have been predicted from the prior art, especially from a reading of Kooistra. Further, this result clearly shows that bases cannot be used interchangeably to obtain identical results.

Further, Applicants submit herewith for the Examiner's consideration a copy of the Journal of Organic Chemistry article (Vol. 35, pp. 2429-2430 (1970)) cited by Kooistra in referencing the use of triethylamine or DMAP in the reaction between the described acid chloride and t-butanol (page 5, line 24 of Kooistra to page 6, line 2). This document only exemplifies the use of triethylamine as a base for the transformation of an acid chloride to an ester (see Examples A and B on page 2430).

For at least the above reasons, Applicants respectfully submit that Kooistra does not render Applicants' claims obvious and therefore that this rejection be withdrawn.

2. Conclusion

All claims are believed to be in proper form in all respects and a favorable action on the merits is respectfully requested. The Examiner is invited to contact the undersigned with any questions or concerns that may prevent this requested allowance.

Except for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application, including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or to credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Dated: **May 9, 2008**
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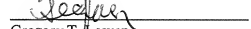

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Chemistry of Cephalosporin Antibiotics. XVIII. Synthesis of 7-Acyl-3-methyl-2-cephem-4-carboxylic Acid Esters

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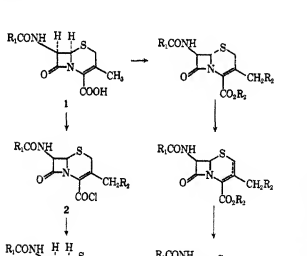
Recent publications[1,2] from these laboratories have described results which constitute the synthesis of a cephalosporin from a penicillin. In this and the following note,[3] we report additional studies of the functionalization of deacetoxymethyl cephalosporins.[2]

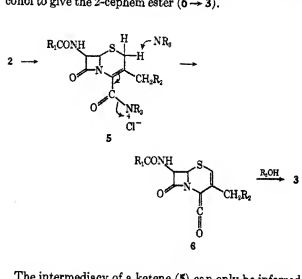
The initial part of the Webber, *et al.*,[2] sequence involves an esterification of the 3-cephem acid **1**, an isomerization, and deesterification to give the 2-cephem acid **4**, which in turn is esterified to give an easily cleavable ester in low overall yield. An alternative preparation of pure 2-cephem esters involving the acid chloride **2** and a probable ketene intermediate is described herein.



Δ^3-Cephalosporanyl chlorides are best prepared in an inert solvent with oxalyl chloride, using N,N-dimethylformamide as a catalyst. Other acid chloride forming reagents, such as thionyl chloride or phosphorus pentachloride, with or without catalysts, are less effective.

The esterification conditions are dependent upon the nature of the alcohol being employed. Tertiary alcohols may be used in excess at ice-bath temperatures; however, primary or secondary alcohols are used preferably in approximately equivalent amounts and at lower temperatures to minimize Δ^2-ester formation. The reaction conditions require that the preformed acid chloride be added slowly to a solution of the alcohol and tertiary amine base in an inert solvent. Some of the esters prepared by this method are listed in Table I. The reaction is limited only by the stability and/or acidity of the alcohol and is readily adaptable to large scale (1 mol) preparations.

The mechanism of the esterification probably involves initial acylation of the tertiary amine. Another molecule of base then removes a proton at C-2, causing a double-bond shift ($\Delta^1 \rightarrow \Delta^2$) and expulsion of the tertiary amine group to give the very reactive ketene (**5** → **6**). The ketene immediately reacts with the alcohol to give the 2-cephem ester (**6** → **3**).



The intermediacy of a ketene (**5**) can only be inferred at this time; however, acid chlorides and amine bases react to give ketenes.[4] Our attempts to isolate an adduct with phenyl isocyanate or tosyl isocyanate[5] have not succeeded. The high reactivity of the intermediate prevented its spectral identification even when generated at low temperatures (−75°).

Van Heyningen and Ahern[6] have recently shown that the 2-cephem acid formed in an equilibrative process (such as that used by Webber, *et al.*[2]) has a C-4 β hydrogen. The same stereochemistry is observed in the reaction described herein; however, the absence of Δ^2 material suggests that the stereochemistry is kinetically controlled. This may be explained by the α-face departure of the tertiary amine base preventing the attack of an alcohol molecule from that side. The alcohol, which may be held in position by a hydrogen bond to the amido hydrogen, would thus add to the β side of the ketene and give the observed stereochemical result.

Experimental Section

Melting points were determined on a Kofler melting point apparatus. Infrared spectra were determined on a Perkin-Elmer

(1) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **88**, 1896 (1963); (b) *ibid.*, **91**, 1401 (1969).

(2) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *ibid.*, **91**, 5674 (1969).

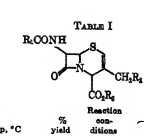
(3) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, in press.

(4) (a) T. Ozaki and M. Kusaka, *Bull. Chem. Soc. Jap.*, **39**, 1995 (1966); (b) T. Ozaki and M. Kusaka, *ibid.*, **40**, 1232 (1967); (c) G. B. Payne, *J. Org. Chem.* **31**, 718 (1966); (d) W. E. Truce and P. S. Bailey, Jr., *ibid.*, **34**, 1341 (1969).

(5) E. Mundlos and R. Graf, *Justus Liebigs Ann. Chem.*, **677**, 108 (1964).

(6) E. M. Van Heyningen and L. K. Ahern, *J. Med. Chem.*, **11**, 933 (1968).

TABLE I



Compd[a]	Registry no.	Empirical formula	Mp, °C	% yield	Reaction conditions	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	24647-38-9	$C_{25}H_{24}N_2O_6S$	78–80	87	A	59.20	5.98	6.93	59.20	6.08	6.63
2	24144-88-5	$C_{32}H_{30}N_2O_6S$	112–114	90	B	61.52	5.16	5.97	61.95	5.33	6.12
3	24647-40-3	$C_{21}H_{22}N_2O_6S$	92–93	85	A	60.86	5.35	6.76	61.02	5.59	7.00
4	24647-41-4	$C_{21}H_{24}N_2O_6S$	83–85	46	A	60.56	5.81	6.73	60.34	6.01	6.91
5	24647-42-5	$C_{24}H_{28}N_2O_6S$	145–146	77	B	61.80	4.75	6.01	62.06	4.97	6.14
6	24647-43-6	$C_{21}H_{21}N_3O_8S$	130	60	B	57.25	4.18	8.70	57.10	4.47	8.45
7	24647-44-7	$C_{21}H_{24}N_2O_6S$	110	45	B	67.89	5.09	5.45	67.82	5.18	5.59
8	24647-45-8	$C_{22}H_{24}N_2O_6S$	130–131	45	B	61.84	6.23	7.21	61.59	6.23	7.04
9	24647-46-9	$C_{21}H_{24}N_2O_6S_2$	178	33	A	53.09	5.35	6.19	53.08	5.33	6.11

[a] 1, R_1 = $PhOCH_2$; R_2 = H; R_4 = $C(CH_3)_3$. 2, R_1 = $PhOCH_2$; R_2 = H; R_4 = $-CH_2-C_6H_4-OCH_3$. 3, R_1 = $PhOCH_2$; R_2 = H; R_4 = $-C(C{\equiv}CH)(CH_3)_2$. 4, R_1 = $PhOCH_2$; R_2 = H; R_4 = $-C(CH{=}CH_2)(CH_3)_2$. 5, R_1 = $PhOCH_2$; R_2 = H; R_4 = $CH_2C(=O)Ph$. 6, R_1 = $PhOCH_2$; R_2 = H; R_4 = $CH_2-C_6H_4-NO_2$. 7, R_1 = $PhOCH_2$; R_2 = H; R_4 = $-CH(Ph)_2$. 8, R_1 = $PhCH_2$; R_2 = H; R_4 = $C(CH_3)_3$. 9, R_1 =  ; R_2 = OAc; R_3 = $C(CH_3)_3$.

Model 21 in a KBr disk. The ultraviolet spectra were measured in methanol solution. The nmr spectra were recorded with Varian Models A-60 and HA-60 spectrometers at 60 MHz in 5–10% deuteriochloroform solution with tetramethylsilane as an internal standard. Elemental analyses were determined by our microanalytical laboratory.

3-Methyl-7-phenoxyacetamido-3-cephem-4-carbonyl Chloride.—A suspension of 0.353 g (1.02 mmol) of 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid in 40 ml of C_6H_6 was cooled in ice and stirred while 0.256 g (2 mmol) of oxalyl chloride and 1 drop of DMF were added. The reaction mixture was stirred at about (7–10°) for 45 min, and then the solvents were removed under reduced pressure. An nmr spectrum of the acid chloride showed the absence of any 2-cephem isomer.

The acid chloride (~200 mg) was dissolved in 10 ml of MeOH and stirred at 25° for 30 min. The solvent was removed, and the residue was redissolved in C_6H_6. The C_6H_6 solution was washed with H_2O, 3% HCl, and 10% $NaHCO_3$. The solution was dried over Na_2SO_4 and evaporated to dryness to give 0.160 g of methyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate. The ester was crystallized from EtOAc and was found to be identical with authentic material[1] by tlc, mp 135–137°, mmp 135–138°.

The acid chloride as prepared above was used in the following preparations. These preparations are presented as typical examples for the esterification of tertiary and primary alcohols, respectively. The esters listed in Table I are prepared analogously.

A. *t*-Butyl 3-Methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate.—A solution of 0.10 mol of the acid chloride (using proportions given above) in 1.0 l. of CH_2Cl_2 was added dropwise over a 3-hr period to a stirred solution of 92.5 g (1.25 mol) of *t*-butyl alcohol (freshly distilled from $KMnO_4$ and dried over molecular sieves) and 19.3 g (0.175 mol) of triethylamine (freshly distilled from phenyl isocyanate and dried over KOH pellets) in 660 ml of CH_2Cl_2 maintained under anhydrous conditions at ice bath temperature. The CH_2Cl_2 solution was washed with about 500 ml of H_2O and 100 ml of 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% $NaHCO_3$ and H_2O, and then treated with 20 g of activated charcoal. The suspension was filtered and evaporated to dryness. The *t*-butyl ester crystallized from ether to give a total yield of 37.5 g (75%) of needles, mp 78–80°. From the neutral and basic washes was recovered 7.0 g of a mixture of Δ^1 and Δ^2 acids.

The nmr spectrum of the Δ^2 ester [δ ($CDCl_3$) C-2 H at 5.92, C-4 H at 4.56, $-OC(CH_3)_3$ at 1.50 ppm] was consistent with the proposed structure.

B. *p*-Methoxybenzyl 3-Methyl-7-(phenoxyacetamido)-2-cephem-4-carboxylate.—A solution of 2 mmol of the acid chloride in 20 ml of alcohol-free $CHCl_3$ was added dropwise over a 1-hr period to a stirred solution of 0.300 g (2.2 mmol) of *p*-methoxybenzyl alcohol and 0.300 g of triethylamine maintained at −50 to −75°. The solution was washed with H_2O and then 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from CCl_4 as needles, mp 108–110°. The nmr spectrum (C-2 H at 5.90, C-4 H at 4.80 ppm) was identical with that of authentic material.[2]

Chemistry of Cephalosporin Antibiotics. XIX. Transformation of Δ^2-Cephem to Δ^2-Cephem by Oxidation–Reduction at Sulfur

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Received September 17, 1969

A recent report from our laboratory details the final steps by which a penicillin can be converted into a cephalosporin.[1] A vital sequence in this synthesis is the conversion of a Δ^2-cephem ester (1) to a Δ^2-cephem ester (3) *via* the sulfoxide 2. This process utilizes the concept that β,γ-unsaturated sulfoxides are thermodynamically more stable than the corresponding α,β-unsaturated sulfoxides.[2]

By contrast, an equilibrium mixture of cephem isomers before oxidation contains largely the unnatural

(1) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Amer. Chem. Soc.*, **91**, 5674 (1969).

(2) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964).